REMARKS

Title of the Invention

The Examiner states that the title of the invention is not descriptive. The Examiner further states that a new title is required that is clearly indicative of the invention to which the claims are directed.

Applicants have amended the title to be clearly indicative of the invention. No new matter has been added by this amendment. Therefore, entry of this amendment into the application is respectfully requested.

Abstract of the Disclosure

The Examiner states that the Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention.

Applicants have amended the Abstract of the Disclosure to more adequately describe the claimed invention and thus, reconsideration and withdrawal of the objection are respectfully requested. No new matter has been added by this amendment. Therefore, entry of this amendment into the application is respectfully requested.

Amendments to the Specification

The Examiner states that the application is to be reviewed and all spelling, trademarks, and like errors corrected.

Applicants have amended the specification to comply with the requirement to indicate trademarks and to update the status of a related application. No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Amendments to the Claims

Applicants have canceled Claims 2 and 6. Applicants have amended Claims 1, 3-5, 7-8 and 11-13 to more particularly point out the claimed subject matter by spelling out "tumor necrosis factor." Support for these amendments is found in the specification, for example, at

page 16, line 9 to line 19. Applicants have revised Claim 4 to recite "a method of treating psoriasis" to be consistent with the title and the remaining claims. Support for this amendment is found thoughout the specification including the originally filed claims.

No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Form U.S. PTO-892

Applicants note that the Examiner has checked off the box on the Office Action Summary indicating that a Form PTO-892 was enclosed. However, Applicants did not receive a Form PTO-892. Applicants request that the Examiner forward Form PTO-892 with the next Office Action.

Interview Summary

Applicants note that the Examiner has checked off the box on the Office Action Summary indicating that a Form PTO-413 was enclosed. However, Applicants did not receive a Form PTO-413. Applicants request that the Examiner forward Form PTO-413 with the next Office Action.

Claims Pending

Applicants note a typographical error in item 2 of the Office Action where the Examiner states that "Claims 1-12 are pending." Applicants wish to clarify that Claims 1-13 were pending.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on October 30, 2001 and Supplemental IDS's were filed on March 29, 2002, August 26, 2002, and October 9, 2002. The Examiner notes in item 3 of the Office Action that the Examiner will provide the Information Disclosure Statements in the next Office Action. Provision of the IDS's is respectfully requested.

Priority

The Examiner states that the filing date of the instant claims is deemed to be the filing date of the priority application 08/570,674, filed 12/11/95, as the previous priority applications do not support the claimed limitations of the instant application, encompassing methods of treating psoriasis.

Applicants respectfully disagree. The instant claims are entitled to priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991). U.S. Application Serial No. 07/670,827 discloses and enables anti-TNF antibodies for treating diseases including "chronic inflammatory diseases." (specification at page 40, line 5). For a clear understanding of the definition of psoriasis, please see Fauci, A. S. *et al.*, Harrison's Principles of Internal Medicine 300 (McGraw-Hill, 14th ed. 1998) (hereinafter "Harrison's") which is attached as Exhibit A. Harrison's teaches that psoriasis is a chronic inflammatory disease. Thus, Applicants are entitled to priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991). This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120.

Enablement of Claims 1, 3-5, and 11-13 Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5, and 11-13 satisfy the requirements of enablement under 35 U.S.C. § 112, first paragraph. The Examiner states that, given the patented claims set forth in U.S. Patent No. 5,698,195 (Le, *et al.*) the requirement for the claimed cA2 antibodies under 35 U.S.C. § 112, first paragraph, enablement, has been satisfied. However, the Examiner states that amendment of the specification to recite deposit information is required. Applicants respectfully disagree.

The antibodies are readily obtainable by the teachings of the specification. Therefore, the biological materials for cA2 antibodies have not been publicly deposited.

Applicants direct the Examiner's attention to the Federal Circuit decision in *In re Wands,* 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (a copy of which is attached hereto as Exhibit B for the Examiner's convenience). The claims at issue in *In re Wands* recited methods for an immunoassay using high affinity monoclonal antibodies that the Appellants found to have unexpectedly high sensitivity and specificity. The position of the PTO was that the data showed

that the production of the antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make them.

As stated by the court in *In re Wands,* 8 U.S.P.Q.2d at 1404, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." The court concluded that undue experimentation would not be required to practice the claimed invention. The court stated that "Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples." *Id.* at 1406. The court further stated that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* The court in *In re Wands* recognized that the nature of monoclonal antibody technology is such that it involves screening hybridomas to determine which ones secrete antibodies with desired characteristics, and that practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. *Id.* The court went on to state that "in the monoclonal art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen." *Id.* at 1407.

In considering the factors enumerated in *In re Wands,* Applicants' disclosure provides considerable direction and guidance on how to practice their invention and presents numerous working examples. In addition, there was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

Applicants' written specification fully enables the practice of the claimed invention because the claimed cA2 antibodies can be made from readily available starting materials using methods that are well known in the art and taught in detail in the specification. The variable regions of the antibodies are disclosed in Figures 16A-16B. In addition, the specification teaches a method of producing the claimed cA2 antibodies according to the present invention (See instant Detailed Description at page 32, lines 7 through 24; page 34, line 10 through page 35, line 4; and Examples III-IX). Additionally, it teaches methods of cloning a polynucleotide encoding an anti-TNF variable or constant region. (See, for example, instant Detailed Description at page 28, line 3 through page 31, line 2). Furthermore, the instant specification teaches that preferred anti-TNF mAbs include those which will competitively inhibit *in vivo* the binding to human TNF-α of anti-TNF-α murine mAb A2, chimeric mAb cA2, or an antibody having substantially

the same specific binding characteristics, as well as fragments and regions thereof. (See, for example, page 19, lines 17-20). It also teaches preferred methods for determining mAb specificity and affinity (See, for example, instant Specification at page 19, line 25 through page 20, line 2, and Examples X and XI). Thus, a person of skill in the art would not be subject to undue experimentation without reasonable expectation of success in order to make and screen cA2 antibodies which would have these claimed elements.

A deposit is not required because the disclosure is sufficient to enable production of the claimed antibodies. No more is required. The Examiner has failed to present any evidence which suggests that anti-TNF antibodies with the claimed specificity are unusually difficult to isolate.

Furthermore, as noted by the Examiner, the claims in the related U.S. patent No. 5,698,195 are enabled. Additionally, this application claims priority to, and incorporates by reference, other applications with substantially the same specification which have issued as patents which were deemed to be in compliance with the 35 U.S.C. § 112, first paragraph enablement requirement for cA2 antibodies (*see, e.g.*, U.S. Patent Nos. 5,656,272; 5,919,452; and 6,284,471). Moreover, Applicants' argument that the claims are enabled and a cA2 deposit is not required has been found persuasive in the related U.S. Application No. 09/756,301.

As discussed above, the instant Specification and figures provide ample teachings such that one of skill in the art would not be subject to undue experimentation in order to make or use the claimed antibodies. Thus, the skilled artisan is enabled to make and use the claimed invention commensurate in scope with the claims.

Rejection to Claims 1-13 Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1, 3-5, and 11-13 as indefinite in the use of "cA2" as the sole means of identifying the claimed antibody. Specifically, the Examiner states that "the use of 'cA2' antibody as the sole means of identifying the claimed antibody renders the claims indefinite because this designation is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct cell lines."

Applicants respectfully traverse this rejection. "cA2" is recognized by those skilled in the art as a unique identifier of Applicants' chimeric monoclonal antibody. A number of scientific articles and press releases refer to Applicants' claimed monoclonal antibody as "cA2." (See, for example, Elliott, M. J., *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis Rheum, 36*:1681-1690 (1993) (Exhibit C); Walker, R.E., "Inhibition of Immunoreactive Tumor Necrosis Factor-alpha by a Chimeric Antibody in Patients Infected with Human Immunodeficiency Virus Type 1," *J. Infect. Dis.*, 174(1):63-8 (1996), abstract from AIDSLINEMED/96261994 (Exhibit D); and "New Monoclonal Antibody Effective Treatment For Crohn's Disease Therapy," *Doctor's Guide* (May 13, 1997), http://www.docguide.com/dg.nsf/PrintPrint/815D53A771190A4285256496004B0796 (Exhibit E)). These articles are representative of the general knowledge of one skilled in the art and demonstrate that the identifier "cA2" clearly defines the claimed product. Moreover, a number of claims have issued which refer to the instant monoclonal antibody as cA2. For example, the claims of related U.S. Patent No. 6,284,471, which has the same priority date as the instant application, recite cA2. (A copy of the claim set of U.S. Patent No. 6,284,471 is attached hereto as "Exhibit F" for the Examiner's convenience). Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner has rejected Claims 1-13 as being indefinite for failing to spell out "TNF" and "hTNF" in the claims. In addition, the Examiner states that the Applicant should indicate tumor necrosis factor "α" as the specificity of the claimed/disclosed antibodies.

Applicants have canceled Claims 2 and 6. Applicants have amended Claims 1, 3-5, 7-8 and 11-13 to spell out the term "TNF" upon the first usage of the terms in the claims. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1-2, 5-6, and 11-12 Under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 1-2, 5-6, and 11-12 under 35 U.S.C. § 102(e) as being anticipated by Adair *et al.* (U.S. Patent No.: 5,994,510). Applicants have canceled Claims 2 and 6.

The Examiner states that:

> Given the properties of the prior art TNFα-specific antibodies which include antibodies that neutralize TNF, including reducing or inhibiting a biological activity of human TNFα as measured by an in vitro or in vivo bioassay (e.g. see Summary of the Invention in column 5) as well as the referenced methods of inhibiting patients suffering disorders associated with undesirably high levels of TNF, including psoriasis (e.g. see columns 1-12, including column 11, line 52) with TNFα-specific antibodies; the claimed functional limitations . . . would be inherent properties of the referenced methods to treat psoriasis with TNFα-specific antibodies.

Applicants respectfully disagree. First, this reference is not eligible as prior art under 35 U.S.C. § 102(e). Applicants note that the priority date of the subject application (March 18, 1991) precedes the 35 U.S.C. § 102(e) date for the Adair reference cited by the Examiner.

Second, even if Adair were eligible as prior art, Adair does not expressly or inherently teach the claimed invention. Applicants' claims recite antibodies which competitively inhibit binding of TNF to cA2. Applicants teach antibodies with high binding affinity for TNFα. Antibodies of the claimed invention, including monoclonal Ab cA2, are high affinity anti-TNF antibodies, and fragments or regions thereof, that have potent inhibiting and/or neutralizing activity *in vivo* against human TNFα. (Specification page 19, lines 7-9).

The Adair reference cited by the Examiner teaches TNFα-specific antibodies, including recombinant chimeric and humanized antibodies, for use in diagnosis and therapy. Further, Adair teaches recombinant antibody molecules having antigen binding sites derived from the murine mAbs CB0006, CB0010, hTNF3 or 101.4.

Adair does not expressly anticipate the claimed invention. Generally, all of the elements of the claimed invention must be found within a single reference in order to anticipate, either expressly or inherently, under 35 U.S.C. §102. As stated in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986) (Exhibit G), for example, "[i]t is axiomatic that for prior art to anticipate under §102 it has to meet every element of the claimed invention, and that such a determination is one of fact." Adair does not teach the chimeric anti-TNF monoclonal Ab cA2 or antibodies which competitively inhibit binding of TNF to cA2. In addition, Adair does not teach antibodies with high binding affinity for TNFα nor does Adair teach antibodies with potent inhibiting affinity for TNFα. The Adair reference does not meet every element of the claimed invention, therefore, the Adair reference does not expressly anticipate the claimed antibodies.

Further, Adair does not inherently teach the claimed invention. The Manual of Patent Examining Procedure (MPEP 8th edition, February 2003 revision, § 2112) articulates the requirements of a rejection based on inherency. Specifically, under the sub-heading **"Examiner Must Provide Rationale for Evidence Tending to Show Inherency,"** the MPEP quotes a decision by the Board of Patent Appeals and Interferences in *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original), which states:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art.

As explained by the MPEP, the Examiner *in Ex parte Levy* argued, without providing support, that a reference inherently included a limitation of the Appellants' invention. According to the MPEP, the Board of Patent Appeals and Interferences reversed the Examiner's decision because the Examiner's assertion was not supported. Specifically, as stated by the MPEP at page 2100-52:

> The Board reversed on the basis that the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.

Further, the doctrine of inherency is based on the necessary presence of an element described in a reference; it is not sufficient to establish that a presence of the element is a probability or a possibility. For example, as is also stated in the MPEP at § 2112 (emphasis in original):

> The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

(Citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993).)

Established case law is replete with examples firmly establishing that inherency is based on the necessary presence of a claimed element. For example, the Court of Appeals for the Federal Circuit has stated in *Continental Can Company v. Monsanto Company*, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991) (emphasis added) (Exhibit H):

> [It] must [be made] . . . clear that the missing descriptive matter *is necessarily present* in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

The Examiner presented no evidence that the antibodies disclosed by Adair would necessarily competitively inhibit chimeric anti-TNF monoclonal cA2 antibodies. Additionally, the Examiner has presented no evidence that the antibodies of Adair would necessarily have a high binding affinity for TNFα.

Applicants' claimed invention does not necessarily flow from the disclosure of Adair. Antibodies have different binding affinities for various epitopes on TNFα, and the biological activity of TNFα is not restricted to one unique site. See, for example, Moeller, A., *et al.*, "Monoclonal Antibodies to Human Tumor Necrosis Factor α: In Vitro and In Vivo Application," *Cytokine, 2*:162-169, 166 (1990) (cited on U.S. PTO Form 1449 on October 30, 1991 as Reference AX4). Moeller described the generation of three murine monoclonal antibodies to human TNFα, designated mAb 114, mAb 195, and mAb 199. *Id.* at 165. Moeller isolated two types of neutralizing monoclonal anti-TNFα antibodies that bind to distinct antigenic epitopes, mAb 195 and mAb 114. *Id.* Moeller discovered that mAb 195 can still bind to its recognized epitope when the TNF occupies the receptor. *Id.* at 166. This suggests that TNFα molecule can be divided into a receptor binding and a neutralization area. *Id.* The second neutralizing antibody, mAb 114, can bind simultaneously with mAb 195 to TNFα. *Id.* The epitope recognized by this monoclonal antibody is related spatially to mAb 199, a non-neutralizing antibody. *Id.* These results demonstrate that antibodies have different binding affinities for various epitopes on TNFα, and the biological activity of TNF is not restricted to one unique site. *Id.*

In addition, as evidenced by Rathjen, not all TNFα antibodies have the same neutralizing properties. *See* Rathjen WO 91/02078 (cited on U.S. PTO Form 1449 on October 30, 1991 as Reference AP2). Rathjen produced panels of monoclonal antibodies active against human TNF and characterized them with respect to their effects on the anti-tumour effect of TNF, TNF receptor binding, activation of coagulation, and defined their topographic specificities. *Id.* at 3. Rathjen shows that different topographic regions of TNF alpha are associated with different activities. *Id.* at 3-4. Rathjen teaches that the activities of anti-TNF mAbs are not necessarily related or linked to each other. *Id.* at Table 2, page 22. Thus, the parameters used for characterizing the claimed antibodies are not features of all TNFα Abs and the claimed antibodies have not been inherently disclosed by Adair.

Therefore, in addition to lack of express disclosure in Adair of the antibodies of Applicants' claimed invention, the Examiner also has not properly met the requirements of a rejection of Applicants' claims based on inherency because the Examiner has not provided evidence or reasoning tending to show inherency in Adair of Applicants' claimed subject matter.

Adair does not expressly or inherently teach human-murine chimeric anti-TNF antibodies, which competitively inhibit monoclonal Ab cA2, and fragments or regions thereof, that have potent inhibiting and/or neutralizing activity *in vivo* against human TNFα with high binding affinity for the specific epitopes on TNFα. Thus, the rejected claims are novel. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1-13 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-13 as being unpatentable over Adair *et al.* (U.S. Patent No.: 5,994,510) in view of Le *et al.* (WO 92/16553). As indicated above, Claims 2 and 6 are canceled. According to the Examiner "given the well known use of therapeutic antibodies that have decreased immunogenicity to overcome neutralizing effects of the immune response in human patients, it had been well accepted practice by the ordinary skill in the art at the time the invention was made to employ therapeutic antibodies [with] decreased immunogenicity, such as chimeric antibodies, humanized antibodies," as taught in Le *et al.* and Adair *et al.* Further, the Examiner states that "...one of ordinary skill in the art at the time the invention was made would have been motivated to modify the anti-TNFα antibodies or the cA2-specific anti-TNFα

antibodies by making them human to decrease immunogenicity in the methods of treating psoriasis with TNFα–specific antibodies taught by Adair *et al.*"

1. Le *et al.* and Adair *et al.* are not prior art

Applicants respectfully disagree. First, Applicants note that the Examiner has cited Applicants' PCT application Le *et al.* (WO 92/16553) as prior art. Le *et al.* (WO 92/16553) is not prior art because Applicants are entitled to a priority date before the PCT application. Specifically, Applicants are entitled to priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991). The PCT (WO 92/16553) was filed March 18, 1992 and also claims the benefit of priority to the same U.S. priority application (U.S. Serial No. 07/670,827) as the subject application. Furthermore, the PCT application is substantially identical to the corresponding U.S. priority application (U.S. Serial No. 07/853,606) of the subject application, which was filed on the same date (March 18, 1992). Hence, Applicants' PCT application Le *et al.* (WO 92/16553) is not prior art.

Furthermore, as stated above, Applicants also note that the priority date of the subject application (March 18, 1991) precedes the priority date for the Adair reference cited by the Examiner. Therefore, Adair is not prior art. In addition, as stated above, Adair does not teach Applicants' antibodies.

2. Prior to the data presented in Applicants' application, there was no reason to believe that a substantial clinical benefit was possible with a chimeric anti-TNF antibody

At the time of filing of the patent application, which claims the benefit of priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991), it was not known that such chimerization of murine antibodies could be done successfully, or that chimeric antibodies provided superior results to murine antibodies for *in vivo* therapy. Further, the use of chimeric antibodies does not eliminate the immunogenic reaction. The presence of non-human sequences in humanized and chimeric antibodies indicates that immunogenicity would still be a concern in therapies involving such antibodies. In fact, most (if not all) chimeric antibodies, similar to murine antibodies, generate an immune response in the administered animal. Thus, it was

unclear, prior to the data presented in this application, that substantial clinical benefit was possible with a chimeric anti-TNF antibody.

In fact, the art at the time of the claimed invention taught *away* from the concept that chimerization prevents an immunologic response against administered antibodies. For example, Brüggemann, M., *et al.*, "The Immunogenicity of Chimeric Antibodies," *J. Exp. Med. 170*:2153-2157 (1989) (Exhibit I) tested allogeneic responses in mice to administered antibodies and found that in a chimeric derivative (in which only the V region frameworks were foreign), an immunologic response to the V region remained and was unattenuated, demonstrating to the authors that "foreign V_H frameworks can be sufficient to lead to a strong antiantibody response." See page 2157. Further, the authors caution that even with *wholly human* antibodies, problems may be encountered with allogeneic responses directed against both the V and C regions. *Id.* at 2156.

Thus, the Brüggemann *et al.* reference further demonstrates unpredictability of clinical administration of chimeric antibody molecules. The authors state in the abstract, "...little is known about the immunogenicity of chimeric antibodies. It is unclear to what extent a particular V domain is characteristic of the species from which it originates, and therefore, whether a response will be elicited by an antibody in which only the V region is foreign." Abstract at 2153. This unpredictability must be considered when determining whether there was sufficient motivation for one of skill in the art to invent the claimed compounds.

The Brüggemann *et al.* reference teaches that it may not be sufficient in a clinical setting, in any meaningful way, to avoid the anti-C region response. Therefore, it teaches away from the use of chimeric antibodies as therapeutic compounds for clinical use, because it teaches that the administration of such antibodies can still lead to a strong immunological response in the patient, hereby rendering such administration clinically inadequate. One of skill in the art would not be motivated to invent a compound intended for a clinical administration which could do more harm to the patient (e.g. due to causing an adverse immune response) than good (due to causing a therapeutic effect). In any event, these references would not motivate one of skill to modify a murine antibody with an expectation of achieving a clinically relevant improvement.

3. There is objective evidence of non-obviousness

Further, even assuming, *arguendo*, that a *prima facie* case of obviousness exists, which it does not, it would be overcome by the objective evidence of nonobviousness. Objective evidence of nonobviousness must be considered, as stated in the MPEP at § 2141:

> Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

The claimed invention has led to unexpected results in relation to the prior art, and has satisfied a long-felt need in the relevant field. The fact that others in the field had tried for years to achieve a result, yet had failed, is evidence that the invention would not have been obvious to those skilled in the art when it was invented.

The claimed compounds have been shown to have unexpected results in terms of the degree of success in clinical studies, particularly in studies involving patients with long-term refractory TNFα-mediated disease. *See* Elliott, M. J., *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis Rheum, 36*:1681-1690 (1993) (Exhibit C) (hereinafter "Elliott"). The magnitude of these results in the treatment of a TNFα-mediated disease could not have been reasonably predicted from the prior art. As noted in Elliott on page 1688, due to multiple and overlapping effects of cytokines such as IL-1 and TNFα and the fact that cytokines induce production of other cytokines and of themselves, there had been pessimism about whether targeting a single cytokine *in vivo* would have any beneficial effect. See also, Trentham, D. M., "Immunotherapy and Other Novel Therapies," *Curr. Opin. Rheumatol., 3*:369-372, 370 (1991) (Exhibit J) ("...the relevance of tumor necrosis factor and the biological outcome of its banishment by a monospecific inhibitor remain in doubt..."); and *Id.* at 371 ("Unidimensional attacks on aberrant immune pathways might have a limited effect on the underlying disease process"). This initial skepticism as to the merits of the invention by experts in the field further establishes the nonobviousness of this invention. MPEP § 2141.

Neither Le *et al.* nor Adair are prior art. Even if Adair were prior art, Adair does not describe or suggest Applicants' chimeric anti-TNF antibodies, does not provide a reasonable expectation of achieving such antibodies having reduced immunogenicity and a therapeutic benefit, and does not reasonably suggest that the unexpected and superior results achieved and described herein were possible. Moreover, the claimed invention has led to unexpected results and clearly satisfies a long felt but unsatisfied need. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

Deirdre E. Sanders
Registration No. 42,122
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: February 25, 2004